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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,341	11/28/2000	Avi J. Ashkenazi	P1805R1	7279

9157 7590 06/02/2003

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	19

DATE MAILED: 06/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,341	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Peri d for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *67-94* is/are pending in the application.

4a) Of the above claim(s) *92-94* is/are withdrawn from consideration.

5)☒ Claim(s) *71,72,74,75,77,78 and 80* is/are allowed.

6)☒ Claim(s) *67-70, 73, 76, 79 and 81-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 67-94 are pending.

2. Applicant's election with traverse of Group XXXV, claims 67-88 (now claims 67-91) drawn to an antibody that binds APRIL polypeptide and hybridoma thereof filed on 3/17/02, is acknowledged.

Applicant's traversal is on the grounds that there is no serious burden on the Examiner to examine the methods of the added claims with the antibodies of Group XXXV. This is not found persuasive because the specific antibodies that specifically bind APRIL polypeptide and the methods of using the antibodies are divergent subject matter have different classification Therefore the methods of treating and APRIL-related pathological condition and the antibodies to APRIL polypeptide are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 92-94 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 67-91 are under examination as they read on an antibody that binds APRIL polypeptide and hybridoma thereof.

5. The specification is objected to because the first line on the top of each page is unreadable due to holes punched thrugh the first line. Appropriate correction is required.

6. The statement of biological deposit, on page 104, line 26 through page 105, line 20, is sufficient to satisfy the requirement for the deposit of the hybridoma that produce the anti-APRIL antibodies 3C6.4.2, 5E11.1.2, 5G8.2.2 and 5E8.7.4, PTA-1347, PTA-1346, PTA-1345 and PTA-1344, respectively under 35 U.S.C. § 112, first paragraph.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 69, 81-88, and 90-91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 69 is indefinite because it is unclear how would a monoclonal antibody comprises the 3C6.4.2 antibody. It is suggested that the claim recites a monoclonal antibody is the 3C6.4.2 antibody.

B. Claims 81-88 are indefinite in the recitation of "a sequence derived from" the specific antibodies because the metes and bounds of said "chimeric" antibody is unclear and ambiguous. It is unclear whether "chimeric" refers to any recombinant antibody construct derived form the specific antibody or to a particular antibody construct. For example, the art distinguishes "chimeric" antibodies as referring to variable (e.g. murine) region - constant region (e.g. human) constructs, from "humanized" antibodies as referring to CDR-grafted antibodies.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 70, 73, 76, 79 and 89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody which specifically bind SEQ ID NO: 8 and the specific monoclonal antibody of 3C6.4.2, 5E11.1.2, 5G8.2.2 and 5E8.7.4 secreted by the PTA-1347, PTA-1346, PTA-1345 and PTA-1344, respectively, a chimeric and a humanized antibody thereof for blocking the APRIL binding to BCMA and to TACI is lacking, does not reasonably provide enablement for any monoclonal antibody which binds to "the same epitope as the epitope" to which the 3C6.4.2, 5E11.1.2, 5G8.2.2 and 5E8.7.4 monoclonal antibody produced by the hybridoma cell line deposited as ATCC accession number PTA-1347, PTA-1346, PTA-1345 and PTA-1344, respectively binds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There is insufficient guidance and direction as to make antibodies, wherein the antibodies binds to the same epitope as the epitope to which the 3C6.4.2, 5E11.1.2, 5G8.2.2 and 5E8.7.4 monoclonal antibody binds.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. The specification on page 93, line 28-38 discloses the preparation of anti-APRIL monoclonal antibodies by immunizing BALB/C mice with Flag-APRIL for use in blocking the APRIL binding to BCMA and to TACI (page 96 lines 1-5). However, the specification fails to provide guidance as to how to determine specifically which other antibodies, specifically antibodies which bind the same epitope to which the 3C6.4.2, 5E11.1.2,

5G8.2.2 and 5E8.7.4 monoclonal antibody binds, would function in blocking the APRIL binding to BCMA and to TACI.

The current state of the art in epitope structure prediction is limited given the noncontiguous amino acid residues constitute most epitopes, and that the dynamics of binding is often not integrated into the epitope prediction equation, making epitope structure prediction a complex four-dimensional problem (see Van Regenmortel, page 464, abstract in particular; Methods: A Companion to Methods of Enzymology 9:465-472, 1996). Van Regenmortel notes that 90% of antibodies raised against intact proteins do not react with any peptide fragment derived from the parent protein indicating that these antibodies are directed to discontinuous epitopes (see page 466, column 1 in particular). In addition Van Regenmortel states that the low success rate of antigenic prediction is due to the fact that predictions concern only continuous epitopes and it is unrealistic to reduce the complexity of epitopes that always possess conformational features to one-dimensional, liner peptide models (see page 467, column 2 in particular). Detailed information regarding the specific epitopes recognized by the instant antibodies 3C6.4.2, 5E11.1.2, 5G8.2.2 and 5E8.7.4 and whether those antibodies would function in blocking the APRIL binding to BCMA and to TACI is lacking. Therefore, predicting which antibodies outside of the antibodies of 3C6.4.2, 5E11.1.2, 5G8.2.2 and 5E8.7.4 in the blocking the APRIL binding to BCMA and TACI is well outside the realm of routine experimentation. A skilled artisan would require guidance, such as information regarding the specific epitope recognition of the antibodies successfully used in the instant invention in order to antibodies other than those directed against Flag-APRIL in a manner reasonably commensurate with the scope of the claims. Thus, it would require undue experimentation of one skilled in the art to practice the claimed invention.

In view of the lack of sufficient guidance in the specification and a limited number of working examples, the unpredictability in the art and the breadth of the claims it would take an undue amount of experimentation for one skilled in the art to practice the invention as claimed.

11. Claims 70, 73, 76, 79 and 89 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an antibody which specifically bind SEQ ID NO: 8 and the specific monoclonal antibody of 3C6.4.2, 5E11.1.2, 5G8.2.2 and 5E8.7.4 secreted by the PTA-1347, PTA-1346, PTA-1345 and PTA-1344, respectively, a chimeric and a humanized antibody thereof for blocking the APRIL binding to BCMA and to TACI is lacking.

Applicant is not in possession of for any monoclonal antibody which binds to "the same epitope as the epitope" to which the 3C6.4.2, 5E11.1.2, 5G8.2.2 and 5E8.7.4 monoclonal

antibody produced by the hybridoma cell line deposited as ATCC accession number PTA-1347, PTA-1346, PTA-1345 and PTA-1344, respectively binds.

Applicant has disclosed only the monoclonal antibodies of 3C6.4.2, 5E11.1.2, 5G8.2.2 and 5E8.7.4; therefore, the skilled artisan cannot envision all the contemplated monoclonal antibodies that bind the same epitope to which the 3C6.4.2, 5E11.1.2, 5G8.2.2 and 5E8.7.4 monoclonal antibody binds recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e2) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the

requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 67-68 and 89 are rejected under 35 U.S.C. 102(b) as being anticipated by WO/9900518 (IDS Ref. # 6, filed 3/17/03), as is evidenced by the specification on page 10, lines 12-15 and Bost et al.

The `518 publicantion teaches a monoclonal antibody, which specifically binds to SEQ ID NO: 2 (claimed APRIL (SEQ ID NO:8)) (page 5, lines 32-35in particular). The referenced monoclonal antibody against SEQ ID NO:2 is the same as claimed antibody which binds to APRIL. As is evidenced in the specification on page 10, lines 12-15, that APRIL polypeptide is SEQ ID NO: 8 (see sequence alignment in particular).

Further the `518 publication teaches a monoclonal antibody that specifically binds to SEQ ID NO:3 (page 5, lines 32-35in particular), wherein SEQ ID NO: 3 has 100% sequence homology with claimed APRIL polypeptide of SEQ ID NO:8 at positions 104-250 (see sequence alignment in particular). Further, antibodies "cross-react" with antigens with homologous amino acid residues. Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not bind to the APRIL polypeptide recited in the claims.

As is evidenced by Bost *et al* that an antibody "cross-reacts", i.e. binds to more than one protein sequence, mean that "specifically bind" with both proteins. Bost et al (Immuno. Invest. 1988 ;17:577-586) describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4-6 residues were identical (see entire document, especially the Abstract and Discussion).

Claim 89 is included because the `518 publication teaches the antibody in a composition (page 45, lines 1-5 in particular).

While the prior art teachings may be silent as to the "blocks binding of said APRIL polypeptide to a TACI receptor or a BCMA receptor" per se; the product used in the reference is the same as the claimed antibody. Therefore "blocks binding of said APRIL polypeptide to a TACI receptor or a BCMA receptor" is considered inherent properties.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to the SEQ ID NO:2 recited in the

claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

14. Claims 67-68 and 89 are rejected under 35 U.S.C. 102(e2) as being anticipated by U.S. Patent No. 6,171,787, as is evidenced by the specification on page 10, lines 12-15 and Bost et al.

The `787 patent teaches a monoclonal antibody, which specifically binds to SEQ ID NO: 2 (claimed APRIL (SEQ ID NO:8)) (col., 4, lines 65 through col., lines 4 in particular). The referenced monoclonal antibody against SEQ ID NO:2 is the same as claimed antibody which binds to APRIL. As is evidenced in the specification on page 10, lines 12-15, that APRIL polypeptide is SEQ ID NO: 8 (see sequence alignment in particular).

Further the `787 patent teaches a monoclonal antibody that specifically binds to SEQ ID NO:3 (col., 4, lines 65 through col., lines 4 in particular), wherein SEQ ID NO: 3 has 100% sequence homology with claimed APRIL polypeptide of SEQ ID NO:8 at positions 104-250 (see sequence alignment in particular). Further, antibodies "cross-react" with antigens with homolgous amino acid residues. Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not bind to the APRIL polypeptide recited in the claims.

As is evidenced by Bost *et al* that an antibody "cross-reacts", i.e. binds to more than one protein sequence, mean that "specifically bind" with both proteins. Bost et al (Immuno. Invest. 1988 ;17:577-586) describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4-6 residues were identical (see entire document, especially the Abstract and Discussion).

Claim 89 is included because the `787 patent teaches the antibody in a composition (col., 36, lines 34-42 in particular).

While the prior art teachings may be silent as to the "blocks binding of said APRIL polypeptide to a TACI receptor or a BCMA receptor" per se; the product used in the reference is the same as the claimed antibody. Therefore "blocks binding of said APRIL polypeptide to a TACI receptor or a BCMA receptor" is considered inherent properties.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to the SEQ ID NO:2 recited in the claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

15. Claims 67 and 68 are rejected under 35 U.S.C. 102(e2) as being anticipated by U.S. Patent No.6,440,694, as is evidenced by the specification on page 10, lines 12-15.

The '694 patent teaches a monoclonal antibody, which specifically binds to SEQ ID NO: 4. (col., 3, lines 48-54 in particular). Reference SEQ ID NO: 4 has 100% homology to the claimed APRIL of SEQ ID NO:8 (see sequence alignment in particular). The referenced monoclonal antibody against SEQ ID NO:4 is the same as claimed APRIL antibody. As is evidenced in the specification on page 10, lines 12-15, that APRIL polypeptide is SEQ ID NO: 8 (see sequence alignment in particular).

While the prior art teachings may be silent as to the "blocks binding of said APRIL polypeptide to a TACI receptor or a BCMA receptor" per se; the product used in the reference is the same as the claimed antibody. Therefore "blocks binding of said APRIL polypeptide to a TACI receptor or a BCMA receptor" is considered inherent properties.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to the SEQ ID NO:2 recited in the claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

16. Claims 71-72, 74-75, 77-78 and 80 are allowable.

17. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

18. **1. Correction of Informalities -- 37 CFR 1.85**

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the

examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
May 30, 2003

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600